REMARKS

Applicant acknowledges that claim 1 remains the only claim pending in the application, other than claims 7-20 which have been withdrawn due to a non-elected invention.

The rejection of claim 1 under 35 USC 103(a) as being unpatentable over Abraham et al (American Journal of Pathology – March 2001, Vol. 158, page 1073) in view of Udatsu et al ((Pediatric Surg Int. 2001 Vol. 17, p. 508), Fujimori et al (Cancer Research 2001 Vol 61, p. 6656), Hacia et al (Genome Research 1998, Vol. 8, p. 1245) and GenBank Accession Number Z19054 is respectfully traversed.

The Examiner indicates that claim 1 is drawn to a microchip which comprises a plurality of oligonucleotides fixed on the surface of a solid matrix, wherein the oligonucleotides detect B-catenin mutations. The Examiner indicates that the probes of SEQ ID Nos.1-121 represented potential missense mutations and deletion mutations of codons 29, 31-35, 37-38, 41, 45 and 48 of the B-catenin gene.

Applicant has amended claim 1 so that it is clear that the microchip detects B-catenin mutations at each of 11 hot spot codons inclusive of codons 29, 31-35, 37-38, 41, 45 and 48, respectively.

It is the discovery and recognition of applicant that the oligonucleotides which are fixed on the surface of the solid matrix are those of SEQ ID Nos.1-121 and that these are not potential missense mutations that the B-oligonucleotides

microchip resides in those of SEQ ID Nos. 1-121 and that the plurality of oligonucleotides will detect in the missense mutations and in-frame deletions at the identified 11 hot spot codons.

The subject invention defined in pending claim 1 is directed to a β-catenin oligonucleotide microchip for detecting β-catenin mutations comprising oligonucleotides fixed on the surface of a solid matrix, wherein the oligonucleotides have the nucleotide sequences of SEQ ID NOs: 1 to 121.

I. Summary of the Cited References

Abraham et al. (American Journal of Pathology March 2001 Vol. 158 p. 1073) disclose that β-catenin gene mutations , i.e., missense mutations in codons 33, 34, 35 and 37, and deletions in codons 28-40, 33-39 and 39-48 have been found in 16 sporadic JNAs (Juvenile nasopharyngeal angiofibromas) (see Table 1).

Udatsu et al. (Pediatric Surg. Int. 2001 Vol. 17 p. 508) report that about 75% of HBs (hepatoblastomas) revealed pathogenic β-catenin gene mutations including missense mutations in codons 32, 34 and 37, and interstitial deletions in codons 5-80, 5-40, 25-32, 35-170 and 3-126 (see Table 1).

Fujimori et al. (Cancer Research 2001 Vol. 61 p. 6656) teach missense mutations in codon 37, 38 and 48 of β-catenin gene associated with gastrointestinal carcinoid tumor cases (see Table 1).

GenBank Accession Number Z19054D3 records the amino acid sequence and nucleotide sequence of human β-catenin protein and gene.

Hacia et al. (Genome Research 1998, Vol. 8 p. 1245) disclose high density arrays of > 90,000 oligonucleuotide probes, 25 nucleotides in length, which were designed to screen for all possible heterozygous germ-line mutations in the 9.17-kb coding region of the large multiexon ATM gene.

II. The Inventiveness of the Present Invention

Contrary to the Examiner's opinion, the art as represented by Abraham et al., Udatsu et al., and Fujimori et al., merely disclose that missense mutations in codons 32, 33, 34, 35, 37, 38 and 48, and interstitial deletions in codons 28-40, 33-39, 39-48, 5-80, 5-40, 25-32, 35-170 and 3-126 of β-catenin gene were detected in several tumors including JNAs, HBs and gastrointestinal carcinoid tumors (see respective Table 1 of the cited references). Further, Udatsu et al. teaches that a single nucleotide change at codon 31 should be regarded as a non-pathogenic polymorphism (see p.511 2nd column 1st full paragraph), and Fujimori et al. report that only an S37A mutation was found when exon 3 of β-catenin including codons 29, 33, 37, 41 and 45 in 26 gastrointestinal carcinoid tumor cases was analyzed (see p.6657 2nd column 2nd paragraph). Therefore, none of the cited references teach or even suggest that codons 29, 31, 41 and 45 are mutational hot spots of β-catenin gene related to tumorigenesis as taught in the subject application and that to detect possible missense mutations at the selected codon areas (codons 29, 31, 41 and

45), the microchip must have nucleotide oligonucleotides with sequences of SEQ ID NOs: 1 to 121.

It should also be noted that Hacia et al. discloses a microarray using 25-mer oligonucleotide probes, in which only the central position (13th nucleotide) is substituted with one of the four nucleotides to screen for all possible heterozygous germ-line mutations (see p.1246 2nd column 3rd paragraph and Figure 1). Therefore, the oligonucleotide probes taught by Hacia et al. are entirely different from those taught by the subject application, in which each position of 3 nucleotides corresponding to each of the identified hot spot codons is substituted with one of the four nucleotides to detect all possible missense mutations or deletion is introduced in the 3 nucleotides corresponding to the hot spot codons to detect in-frame shift (see p. 5 line 5 to p. 7 line 19, and p. 14 Table 1a to p.18 Table 1f). In other words, Hacia et al. fail to teach or imply the preparation of an oligonucleotide microchip or the design of oligonucleotides fixed thereon for the detection of β-catenin mutations at such mutational hot spots. Hacia et al. only describe a microarray for screening heterozygous germ-line mutations in a large gene displaying complex mutational spectrum.

Accordingly, even if the teachings of Abraham et al., Udatsu et al., and Fujimori et al. are combined with the GenBank record in view of Hacia et al., a person skilled in the art would think of an oligonucleotide microchip capable of detecting only heterozygous germ-line mutations at codons 32, 33, 34, 35, 37, 38 and 48 of β-catenin gene, which have not been reported to be identified in tumors.

Further, such oligonucleotide microchip derived from all of these teachings cannot detect all missense mutations and in-frame deletions at the 11 mutational hot codons (codons 29, 31, 32, 33, 34, 35, 37, 38, 41, 45 and 48).

On the other hand, the subject invention is based upon the discovery and recognition that codons 29, 31, 41 and 45 besides the 7 codons described by Abraham et al., Udatsu et al., and Fujimori et al. are also the mutational hot spots of β-catenin gene, and it has designed oligonucleotides to detect in-frame deletions (3-bp deletion) as well as all possible missense mutations at the 11 codons.

Since the oligonucleotides used in the oligonucleotide microchip of the subject invention are designed to detect all possible missense mutations at 11 codons, as identified in claim 1, and that they are capable of detecting any missense mutation at these codons. Further, the oligonucleotide microchip of the subject invention also includes the oligonucleotides for detecting in-frame deletion at each of the identified hot spot codons. Namely, the 121 types of oligonucleotides thus designed cover all substitutions and in-frame deletions in the 11 codons of exon 3, which provides improved accuracy and efficiency in detecting β-catenin gene mutation. This is clearly supported in the Specification.

In conclusion, the references are silent as to which oligonucleotide types should be used for the detection of all possible missense mutations and in-frame deletions at each of the 11 hot spot codons according to the subject invention.

Accordingly, it is submitted that the subject invention is not obvious over the combination of all teachings of the cited references.

For all of the above reasons claim 1 is patentable over the cited references.

Respectfully submitted
Attorney for Applicant,

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By: _____
Eugene Lieberstein
Registration No. 24,645

CUSTOMER NO. 01109

ANDERSON KILL & OLICK, P.C.
1251 Avenue of the Americas
New York, New York 10020-1182
(212) 278-1000

CERTIFICATE OF TRANSMISSION

I hereby certify that this *Amendment* is being deposited via EFS-Web and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on May 29, 2007.

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